Human Reproduction, Vol.27, No.5 pp. 1292–1299, 2012
Advanced Access publication on March 14, 2012 doi:10.1093/humrep/des073

human reproduction

ORIGINAL ARTICLE *Gynaecology*

The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres

Steven Simoens[1], Gerard Dunselman[2], Carmen Dirksen[3], Lone Hummelshoj[4], Attila Bokor[5], Iris Brandes[6], Valentin Brodszky[7], Michel Canis[8], Giorgio Lorenzo Colombo[9], Thomas DeLeire[10], Tommaso Falcone[11], Barbara Graham[12], Gülden Halis[13], Andrew Horne[14], Omar Kanj[8], Jens Jørgen Kjer[15], Jens Kristensen[15], Dan Lebovic[10], Michael Mueller[16], Paola Vigano[17], Marcel Wullschleger[16], and Thomas D'Hooghe[18,*]

[1]Katholieke Universiteit Leuven, Leuven, Belgium [2]Department of Obstetrics & Gynaecology, Research Institute GROW, Maastricht University Medical Centre, Maastricht, The Netherlands [3]Maastricht University Medical Centre, Maastricht, The Netherlands [4]World Endometriosis Research Foundation, London, UK [5]Semmelweis University, Budapest, Hungary [6]Medizinische Hochschule Hannover, Hannover, Germany [7]Corvinus University, Budapest, Hungary [8]University Hospital Centre, Clermont-Ferrand, France [9]University of Pavia, Pavia, Italy [10]University of Wisconsin, Madison, WI, USA [11]Cleveland Clinic, Cleveland, OH, USA [12]NHS National Services Scotland, Edinburgh, Scotland [13]Praxis für Fertilität-KEZ-Berlin, Berlin, Germany [14]University of Edinburgh, Edinburgh, Scotland [15]University of Copenhagen, Copenhagen, Denmark [16]University of Bern, Bern, Switzerland [17]University of Milan, Milan, Italy [18]Department of Obstetrics and Gynecology, Leuven University Fertility Center, University Hospitals Leuven, UZ Gasthuisberg, 3000 Leuven, Belgium

*Correspondence address. Tel: +32-16-343624; Fax: +32-16-344368; E-mail: thomas.dhooghe@uz.kuleuven.ac.be

Submitted on April 18, 2011; resubmitted on January 18, 2012; accepted on February 8, 2012

BACKGROUND: This study aimed to calculate costs and health-related quality of life of women with endometriosis-associated symptoms treated in referral centres.

METHODS: A prospective, multi-centre, questionnaire-based survey measured costs and quality of life in ambulatory care and in 12 tertiary care centres in 10 countries. The study enrolled women with a diagnosis of endometriosis and with at least one centre-specific contact related to endometriosis-associated symptoms in 2008. The main outcome measures were health care costs, costs of productivity loss, total costs and quality-adjusted life years. Predictors of costs were identified using regression analysis.

RESULTS: Data analysis of 909 women demonstrated that the average annual total cost per woman was €9579 (95% confidence interval €8559–€10 599). Costs of productivity loss of €6298 per woman were double the health care costs of €3113 per woman. Health care costs were mainly due to surgery (29%), monitoring tests (19%) and hospitalization (18%) and physician visits (16%). Endometriosis-associated symptoms generated 0.809 quality-adjusted life years per woman. Decreased quality of life was the most important predictor of direct health care and total costs. Costs were greater with increasing severity of endometriosis, presence of pelvic pain, presence of infertility and a higher number of years since diagnosis.

CONCLUSIONS: Our study invited women to report resource use based on endometriosis-associated symptoms only, rather than drawing on a control population of women without endometriosis. Our study showed that the economic burden associated with endometriosis treated in referral centres is high and is similar to other chronic diseases (diabetes, Crohn's disease, rheumatoid arthritis). It arises predominantly from productivity loss, and is predicted by decreased quality of life.

Key words: endometriosis / cost-of-illness / quality of life / international / multi-centre

Introduction

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction (Kennedy *et al.*, 2005). Estimates of the prevalence of endometriosis among the general population of women of reproductive age vary between 2 and 10% [reviewed by Eskenazi and Warner (1997), based on original articles by Houston *et al.* (1987), Wheeler (1989), Vessey *et al.* (1993) and Kjerulff *et al.* (1996)]. This prevalence can rise to 30–50% in women with infertility and/or pain (Gruppo italiano per lo studio dell'endometriosi, 1994; Meuleman *et al.*, 2009). Endometriosis is associated with dysmenorrhoea, pain at ovulation, dyspareunia, abnormal bleeding, chronic pelvic pain, fatigue and infertility, yet is often under-diagnosed (Kennedy *et al.*, 2005). Medical or surgical treatments aim to manage symptoms, and to remove or reduce physical disease.

In a society where spiralling health care costs and limited resources are of increasing concern, public policy makers and health care payers need to pay attention to the costs of endometriosis. Cost studies of endometriosis allow the identification of the drivers of diagnosis costs and treatment costs. In addition, cost data can be fed into economic evaluations assessing the cost-effectiveness of approaches to earlier diagnosis and treatment of endometriosis.

The endometriosis-associated costs to society are considerable yet poorly identified. Three recent review papers have emphasized the lack of research on costs of endometriosis and identified several avenues for future research, which our study seeks to address (Gao *et al.*, 2006a,b; Hummelshoj *et al.*, 2006; D'Hooghe *et al.*, 2008). To close the gaps identified in the review papers, the World Endometriosis Research Foundation (WERF) EndoCost study aims to calculate the costs of women with endometriosis treated in referral centres. This approach is combined with an assessment of endometriosis-related quality of life in participating patients. The cost estimates provided by this cost-of-illness analysis may be used to justify the prioritization of future research in endometriosis.

Materials and Methods

The methods of the WERF EndoCost study are reported in detail elsewhere (Simoens *et al.*, 2011), but the main methods are summarized here.

Design

Prospective questionnaires were designed to enable the collection of information on costs and quality of life related to endometriosis-associated symptoms during October and November 2009. These 2 months were chosen as they were considered to be a representative period to study endometriosis-associated symptoms and as they fall outside any religious holiday period. As is the usual practice in cost-of-illness analyses, data were collected over 2 months and results were then extrapolated to an annual time-frame (Simoens *et al.*, 2007).

Setting

A research network, the WERF EndoCost Consortium, was established in 2007 comprising 12 representative tertiary care centres from 10 countries. The definition of a representative centre was based on the recognition of this centre as a referral centre for women with endometriosis-associated symptoms within and outside a country. For each country, one or more gynaecologists and one health economist with a major interest in endometriosis participated in the network.

Participants

The study population included women with a laparoscopic and/or histological diagnosis of endometriosis, who had at least one contact with the treating centre due to endometriosis-associated symptoms during the calendar year of 2008. The diagnosis of endometriosis was not necessarily made in this time period, but could have been made earlier. The study excluded women with suspected endometriosis and women with a history of endometriosis who came to the hospital for a clinical problem unrelated to the disease. Ethical approval was obtained from the ethical committee of each participating centre. Women were required to sign an informed consent form in order to participate in the study.

Perspective

The WERF EndoCost Study measured costs from the societal perspective. This means that costs included direct health care costs (e.g. costs of medication, physician visits, monitoring tests, hospitalization, surgery and informal care provided by family/friends) as well as direct non-health care costs (e.g. transportation costs, costs of support with household activities). Indirect costs of productivity loss due to endometriosis and its treatment were also included.

Data measurement

Cost questions were developed specifically for the purpose of the WERF EndoCost study by the participating health economists and gynaecologists. Questionnaires were piloted and reviewed for face and content validity by the members of the WERF EndoCost Consortium and by six women at University Hospitals Leuven, Belgium. Questionnaires were translated into the local language of each participating country.

Questionnaires elicited demographic characteristics and year of endometriosis diagnosis. Endometriosis was staged at the time of diagnosis based on hospital records using the r-AFS score (1985). Questionnaires also elicited data about the volume of resource use relating to physician consultations, medication, monitoring tests, hospitalizations (i.e. hotel service), surgical procedures, other therapies, support with household activities and informal care. Productivity loss was measured using the Work Productivity and Activity Impairment Questionnaire (Reilly *et al.*, 1993). This generic instrument considered the time lost from work ('absenteeism') as well as reduced productivity at work ('presenteeism') within the past week.

To register the evolution of health-related quality of life over time, the EuroQol-5D instrument was filled in by women at the beginning of the study, at 4 weeks and at 8 weeks (EuroQol Group, 1990). The EuroQol-5D is a generic instrument that contains five dimensions of health-related quality of life: mobility, self-care, daily activities, pain/discomfort and anxiety/depression. Each dimension can be rated at three levels: 'no problems', 'some problems' and 'major problems'. The five dimensions together represent the health state.

Data valuation

Prices reflected charges based on official list prices in all countries, except for the Netherlands and the UK where unit costs based on actual resource use were applied. Prices included the contribution of the third-party payer and the woman's co-payment. Productivity loss was valued using national estimates of gross weekly earnings. Each participating country's health economist was responsible for collecting the price data using a

standardized form in collaboration with the gynaecologist. Price data were derived from national documents and local sources in each country (references are available from the corresponding author on request).

Utility values were assigned to the EuroQol-5D health states using national health utility indices (Dolan *et al.*, 1995; Greiner *et al.*, 2005; Lamers *et al.*, 2006; Shaw *et al.*, 2007; Cleemput *et al.*, 2008). In the absence of a national index for Denmark, France, Hungary, Italy and Switzerland, utility values were derived from a representative sample of the UK population using the time trade-off technique (Dolan *et al.*, 1995). Utility values were combined with estimates of the time period for which a particular health state lasts to compute quality-adjusted life years. The quality-adjusted life year is an outcome measure that accounts for the quantity and quality of life, and that allows for comparison of outcomes between diseases. Quality-adjusted life years were calculated by means of the area under the curve. Quality-adjusted life years were calculated for women who reported a utility value at least at the beginning of the study and at 8 weeks.

Sample size

As is usual practice in cost-of-illness analyses, this study was designed to measure costs rather than test a specific hypothesis about costs and, therefore, no sample size calculation was conducted. Each referral centre identified eligible women and invited them on 31 August 2009 to participate in the study. A total of 3216 women received letters and 1450 provided informed consent in time to be mailed the questionnaires on 24 September 2009. This sample size is larger than previous studies on the costs of endometriosis, which tended to include only a few hundred women (Simoens *et al.*, 2007).

Analysis

Data collection and input into the central database were carried out in each participating centre. If resource use was not applicable or not known, a conservative approach was adopted by setting the associated cost equal to zero. Each centre had the opportunity to contact women to supplement answers for missing values. An analysis checked whether women with missing data were comparable to women with a complete data set in terms of woman characteristics. As this was the case, it was assumed that data of complete cases were representative for women who had missing data, and missing data were dealt with using the mean imputation technique. Overall quality assurance of data entry and data analysis was carried out by the co-ordinating health economist (S.S.).

Costs per woman were computed by multiplying resource use by unit costs. Costs per woman were described as mean ($\pm$standard deviation), minimum/maximum and as 95% confidence intervals (CIs). Total costs were broken down into major cost drivers. Cohen's kappa coefficient was applied to explore the possible evolution of EuroQol-5D scores over the 2-month course of the study. Costs were expressed in euro (1 euro = 1.40 US$ on 25 October 2010). For those countries that did not have the euro as their national currency, costs were converted into euro using purchasing power parity exchange rates (Organisation for Economic Co-operation and Development, 2009). The price year was 2009. Estimates of costs and health-related quality of life during October and November 2009 were multiplied by six to generate annual estimates.

A regression analysis assessed the effect of demographic, clinical and socio-economic characteristics as well as quality of life on total costs and on direct health care costs. Due to non-normality, cost data were log-transformed. Data may be clustered per country and, therefore, a multilevel regression analysis was conducted including country as a random effect. Given that this analysis indicated that country had an effect on costs (although this was not statistically significant), a multivariate regression analysis was run including dummy variables representing specific countries. A backward method to select independent variables was applied, with the final model being restricted to variables significant at the 5% level.

Results

Of 3216 women invited to participate in the study, 1450 provided informed consent and had questionnaires posted to them. Of these women, 909 returned the questionnaires (response rate of 28%; demographic data in Table I). Average total annual costs amounted to €9579 per woman (95% CI: €8559–€10 599) (see Table II). Total costs were dominated by indirect costs of productivity loss (mean: €6298 per woman; 66% of total costs). Direct costs were made up of health care costs (€3113 per woman; 95% of direct costs) and non-health care costs (€168; 5% of direct costs). The most important items of health care costs were surgery (29% of health care costs), monitoring tests (19%), hospitalization (18%) and physician visits (16%). Medication accounted for 10% of health care costs.

Regarding health-related quality of life, 16% of women reported (some or major) problems with mobility, 3% reported problems with self-care, 29% reported problems with usual activities, 56% reported problems with pain/discomfort and 36% reported problems with anxiety/depression at the beginning of the study. EuroQol-5D utility scores varied little over the 2-month course of the study (kappa coefficient: 0.367–0.484; $P < 0.001$). Women with endometriosis-associated symptoms generated an average of 0.809 quality-adjusted life years (standard deviation: 0.193; minimum: −0.080; maximum: 1) over the course of 1year. This represents a reduction in quality of life of 19% when compared with a person with the best possible health state. Only 24% of women generated a quality-adjusted life years of 1.0, indicating that they had the same quality of life as a person with the best possible health state. Two women had negative quality-adjusted life years, implying that they considered their current state of health to be worse than death.

Table III shows that quality of life was the most important predictor of total costs and of health care costs. Furthermore, a more severe stage of endometriosis, the presence of pelvic pain symptoms, the presence of infertility and a higher number of years since diagnosis were associated with higher direct health care costs, after adjusting for country. Conversely, an inability to work due to reasons other than endometriosis, a higher age, a higher number of years since first seeking medical help and a higher body mass index were associated with lower direct health care costs. Some of these variables also predicted total costs. Similar results were obtained when a logistic regression analysis was conducted on patients without costs when compared with patients with positive costs and when a multivariate regression analysis was restricted to patients with positive costs.

Discussion

The WERF EndoCost study has shown that the costs of women with endometriosis treated in referral centres are substantial, resulting in an economic burden that is at least comparable to the burden associated with other chronic diseases. We demonstrate that the annual health care costs of €3113 per woman suffering from endometriosis-associated symptoms and treated in referral centres are similar to the estimated annual (2009) health care costs for diabetes mellitus

Table I Characteristics of women.

Characteristic	Mean (standard deviation)	Minimum–Maximum	Number of women for which data are available
Age (years)	36.1 (6.7)	15–67	905
Height (cm)	166.7 (7.1)	135.6–194.7	901
Weight (kg)	72.1 (27.7)	41–230	889
Current marital status; number of women (%)			904
Single and living with partner	200 (22)		
Married	513 (57)		
Single and not living with partner	123 (14)		
Divorced/separated	67 (7)		
Widowed	1 (0)		
Ethnic origin; number of women (%)			819
Asian/Oriental	17 (2)		
Black African	1 (0)		
African American	5 (1)		
Black Caribbean	2 (0)		
Hispanic or Latino	3 (0)		
North/West European	516 (63)		
East European	84 (10)		
South European	86 (10)		
North American white	75 (9)		
Other white	21 (3)		
Mixed race	9 (1)		
Occupation; number of women (%)[a]			891
Employee	680 (76)		
Self-employed	77 (9)		
Housewife/carer	65 (7)		
In education	44 (5)		
Voluntary work	27 (3)		
Unable to work due to endometriosis	29 (3)		
Unable to work due to other reasons	50 (6)		
Number of years since diagnosis	6.4 (6.3)	0–45	887
r-AFS stage; number of women (%)			706
Minimal-mild (stages I–II)	200 (28)		
Moderate-severe (stages III–IV)	506 (72)		

[a]Percentages do not add up to 100% because women may have multiple occupations.

(€2858), Crohn's disease (€3100–€7447) and rheumatoid arthritis (€4284) in selected European countries (Leardini *et al.*, 2002; Koster *et al.*, 2006; Yu *et al.*, 2008). In addition, we show that the indirect costs of productivity loss are twice as large as the direct health care costs of endometriosis-associated symptoms, also similar to other chronic diseases such as ankylosing spondylitis (productivity loss = 66% of total costs) and rheumatoid arthritis (productivity loss = 57% of total costs) (Franke *et al.*, 2009).

The design of the EndoCost study conceivably either over- or underestimates the economic burden of endometriosis. On the one hand, the study may have overestimated the economic burden of endometriosis, because women with more difficult cases of endometriosis may be more likely to be treated in referral centres and are likely to have a higher consultation rate and, hence, higher costs. On the other hand, the possibility that the study has underestimated the economic burden associated with endometriosis cannot be excluded since the study did not measure any burden related to cost or quality of life before and during the initial surgical diagnosis and treatment of endometriosis prior to any referral to the centres included in the study. This burden is likely to be significant due to the fact that surgery accounts for most of the direct health care costs of endometriosis and due to the well-documented long diagnostic delays between initial symptoms and laparoscopic diagnosis of endometriosis (Kennedy *et al.*, 2005).

It is a challenge to extrapolate the costs reported in this study to national estimates of endometriosis-related costs for two reasons.

Table II Annual costs of endometriosis-associated symptoms (in euro) ($n = 909$).

Item	Mean	Standard deviation	Minimum	Maximum	95% CI of the mean
Direct health care costs	3113.1	13 244.1	0	290 420.4	2251.0–3975.3
Physician visits	513.3	1331.9	0	12 906.0	426.6–600.0
Medication	320.3	1364.2	0	23 843.3	231.5–409.1
Monitoring tests	596.4	2087.7	0	31 224.0	460.5–732.3
Surgery	899.3	10 801.1	0	167 426.0	196.2–1602.4
Other treatments	153.2	741.1	0	15 114.7	104.9–201.4
Informal care	84.0	623.2	0	11 610.0	43.4–124.5
Hospitalization	546.7	3614.1	0	53 644.2	311.5–782.0
Direct non-health care costs	167.8	481.5	0	5983.2	136.5–199.2
Transportation	102.4	321.0	0	5983.2	81.5–123.3
Support household activities	65.4	350.3	0	5310.6	42.6–88.2
Direct costs	3281.0	13 336.4	0	292 286.4	2412.9–4149.1
Indirect costs	6298.3	7262.6	0	39 120.0	5825.6–6771.1
Total costs	9579.3	15 666.8	0	298 584.7	8559.5–10 599.1

For Germany, hospitalization costs related to the costs of the diagnosis-related group associated with a hospital stay.

Table III Multivariate regression analysis of log-transformed costs.

Independent variable	Direct health care costs		Total costs	
	Coefficient (standard error)	*P*-value	Coefficient (standard error)	*P*-value
Constant	12.645 (0.894)	<0.001	13.790 (0.768)	<0.001
Unable to work for reason other than endometriosis	−1.409 (0.478)	0.003	−1.637 (0.455)	<0.001
r-AFS score	0.733 (0.239)	0.002	—	
Presence of pelvic pain symptoms	0.436 (0.171)	0.011	0.456 (0.164)	0.006
Presence of infertility	0.561 (0.229)	0.014	0.683 (0.217)	0.002
Annual number of quality-adjusted life years	−5.029 (0.580)	<0.001	−5.051 (0.557)	<0.001
Age	−0.110 (0.017)	<0.001	−0.078 (0.016)	<0.001
Number of years since diagnosis	0.047 (0.020)	0.018	—	
Number of years since first medical help	−0.001 (0.001)	0.046	—	
Body mass index	−0.049 (0.016)	0.003	—	
Belgium	−0.926 (0.449)	0.040	−0.641 (0.432)	0.138
Denmark	1.098 (0.507)	0.031	0.114 (0.468)	0.808
Germany	2.367 (1.081)	0.029	0.340 (0.426)	0.425
Hungary	−0.281 (0.507)	0.579	1.399 (0.484)	0.004
Italy	1.135 (0.484)	0.019	0.716 (0.465)	0.124
Netherlands	−0.625 (0.444)	0.159	−0.526 (0.427)	0.218
Switzerland	1.991 (0.712)	0.005	0.333 (0.679)	0.624
UK	−0.557 (0.568)	0.328	0.128 (0.545)	0.815
USA	1.444 (0.731)	0.049	−0.656 (0.541)	0.226
$n = 909$				
R^2	0.202		0.168	
Adjusted R^2	0.185		0.154	
F-test on regression model	Value = 11.988; $P < 0.001$		Value = 12.386; $P < 0.001$	

Firstly, there is uncertainty about the prevalence of endometriosis, which has been reported to vary between 2 and 10% [(reviewed by Eskenazi and Warner (1997), based on original papers Houston *et al.* (1987), Wheeler (1989), Vessey *et al.* (1993) and Kjerulff *et al.* (1996)]. However, arguably the best evidence seems to point towards a prevalence rate of 7% (Treloar *et al.*, 1999), based on a study in Australian twins representative for the general Australian population with respect to age, marital status, level of education and ethnicity. Secondly, because of poor reporting in most countries of the diagnosis 'endometriosis' (as opposed to its associated symptoms), no prevalence figures exist which allow us to extrapolate costs for women treated in referral centres and compare these with costs for all women with endometriosis-associated symptoms. Indeed, the methods of inclusion employed in this study could imply that women with moderate-severe endometriosis are over-represented in the patient sample because women were enrolled in representative tertiary care centres that typically treat more complex and referred cases of endometriosis, than those being treated by their general gynaecologists, though the latter may have a higher rate of repeat consultations due to lack of resolvement of symptoms. Furthermore, we must recognize that with a diagnostic delay of ~7 years (Nnoaham *et al.*, 2011), there is a large population of women in our society not being treated at all, and thus losing time to work and using over-the-counter medicine, etc, which would add to these costs if were they being treated adequately. Whereas we recognize that the response rate was low (28%) and the subsample of women who participated in the study may have been highly motivated to answer the questions, possibly because they were more symptomatic than the non-responders, conversely, non-responders may have not participated because they did not want a daily or weekly reminder of the impact of their disease. Finally, since the proportion of women with minimal-mild (28%) and moderate-severe (72%) endometriosis in this study was comparable to the proportion of minimal-mild (37%) and moderate-severe (63%) surgically diagnosed endometriosis in the whole Icelandic population over a 20-year period (Gylfason *et al.*, 2010); this patient population appears to be representative of the overall population with surgically diagnosed endometriosis. We acknowledge, however, that this does not imply that symptoms, treatments and costs are similar and that extrapolating costs in tertiary care centres to national cost estimates remains problematic and a challenge.

In view of the limitations associated with the extrapolation of costs for women with endometriosis in tertiary care referral centres to national cost estimates, only a theoretical model is possible at present, based on reasonable assumptions, which is adaptable to various prevalence rates. In this theoretical model, extrapolation of centre-specific costs to national cost estimates was calculated as follows: annual average (in)direct costs per woman × national number of women of reproductive age (i.e. 15–49 years of age) (World Bank, 2010) × estimated prevalence of endometriosis among women of reproductive age. In our theoretical model, we chose a prevalence of 7%, based on the best available evidence (Treloar *et al.*, 1999) outlined above. Using this theoretical model, the total annual societal burden of endometriosis-associated symptoms can be extrapolated to €0.8 million in Denmark, €1.3 billion in Switzerland, €1.6 billion in Hungary, €1.7 billion in Belgium, €2.6 billion in the Netherlands, €9.3 billion in Italy, €9.5 billion in France, €9.9 billion in the UK, €12.5 billion in Germany and €49.6 billion in the USA. This theoretically calculated extrapolation of centre-specific costs to national cost estimates can be easily re-calculated if a differently justified estimated prevalence rate is applied.

In terms of health-related quality of life, women in our study who suffered from endometriosis-associated symptoms reported mostly problems on the pain/discomfort, depression/anxiety and usual activities dimensions of the EuroQol-5D. This finding is consistent with a literature review (Gao *et al.*, 2006a,b) and with recently published papers (Fourquet *et al.*, 2011; Nnoaham *et al.*, 2011), concluding that endometriosis impairs health-related quality of life especially in the domains of pain, psychological and social functioning. On average, our population had 0.81 quality-adjusted life years over the course of 1 year, which is worse than the 0.85–0.94 quality-adjusted life years per year observed in the general population (Kind *et al.*, 1999; Luo *et al.*, 2005; Bernert *et al.*, 2009). In fact, the decrement in quality of life when compared with the general population generally exceeds the minimally (clinically) important difference (Jaeschke *et al.*, 1989) of 0.07 as calculated for the EuroQol-5D (Walters and Brazier, 2005).

The regression analysis indicated that quality of life represents the most important predictor of total costs and of direct health care costs: a lower number of quality-adjusted life years resulted in higher total costs and in higher direct health care costs. Owing to the explorative character of the regression analysis, no *a priori* hypothesis was formulated regarding the expected direction of the relation between the factors studied and costs. The specific relation between predictors in the model and costs needs further exploration in future costing studies in endometriosis. Although our analysis resulted in a low R^2, similar R^2 values have been observed in other regression analyses of costs (Mackin *et al.*, 2011; Ying *et al.*, 2011).

The true cost of a disease is measured by the additional burden imposed by that disease on society. Therefore, the questionnaires emphasized that women should report resource use based on endometriosis-associated symptoms only. Ideally, a case–control study design could have been used but due to practical and resource constraints, the WERF EndoCost study did not include a control population of women without endometriosis as is also the case in most other cost-of-illness analyses.

Considering our results, it could be possible to set up studies that estimate the cost-effectiveness of primary and secondary prevention of endometriosis. As the primary objective of this article was to present the aggregate results of the first international analysis, this article did not compare costs and quality of life associated with endometriosis between countries. The burden of endometriosis is likely to vary between countries due to, among other things, differences in the access to and financing of, health care systems.

Acknowledgements

The authors thank Katja Kleine-Budde, Annalisa Abbiati, Lynn Borzi, Lianna Christensen, Aisha De Graaff, Diane DeMonaco Dowd, Helen Dewart, Andreas Ebert, Jill McNaughton, Donel Murphy, Paolo Vercellini, Myriam Welkenhuysen and Cheryl Williams for contributing to the data input.

Authors' roles

S.S., T.D'H., L.H., C.D. and G.D. conceived and designed the EndoCost study, analysed and interpreted the data, wrote the first draft of the manuscript and supervised the study. All other authors were involved in the data collection and critical revision of the manuscript, and provided technical support.

Funding

The EndoCost study is funded by the World Endometriosis Research Foundation (WERF) through grants received from Bayer Pharma AG, Takeda Italia Farmaceutici SpA, Pfizer Ltd and the European Society of Human Reproduction and Embryology (ESHRE). The sponsors did not have a role in the design and conduct of the study, the collection, management, analysis and interpretation of the data or in the preparation, review or approval of the manuscript.

Conflict of interest

L.H. is the chief executive and T.D'H. is a former board member of WERF. L.H. and T.D'H. act as consultants to Bayer Pharma AG. T.D'H. holds the Merck-Serono Chair in Reproductive Medicine and Surgery, and the Ferring Chair in Reproductive Medicine at the Katholieke Universiteit Leuven in Belgium and has served as consultant/research collaborator for Merck-Serono, Schering-Plough, Astellas and Arresto.

References

Revised American Fertility Society classification of endometriosis: 1985. *Fertil Steril* 1985;**43**:351–352.

Bernert S, Fernandez A, Haro JM, Konig HH, Alonso J, Vilagut G, Sevilla-Dedieu C, de Graaf R, Matschinger H, Heider D *et al.* Comparison of different valuation methods for population health status measured by the EQ-5D in three European countries. *Value Health* 2009;**12**:750–758.

Cleemput I, Van Wilder P, Vrijens F, Huybrechts M, Ramaekers D. Richtlijnen voor farmacoeconomische evaluaties in België. In: *Federaal Kenniscentrum voor de Gezondheidszorg*. Brussels: Federaal Kenniscentrum voor de Gezondheidszorg, 2008, 1–92.

D'Hooghe T, Vodolazkaia A, Kyama C, Mwenda J, Simoens S. Health economics of endometriosis. In: Rombauts L, Tsaltas J, Maher P, Healy D (eds). *Endometriosis 2008*. USA: Blackwell Publishing, 2008, 1–16.

Dolan P, Gudex C, Kind P, Williams A. A social tariff for EuroQol: results from a UK general population survey. Centre for Health Economics, University of York, York, 1995, 1–24.

Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 1997;**24**:235–258.

EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy* 1990; **16**:199–208.

Fourquet J, Baez L, Figueroa M, Iriarte RI, Flores I. Quantification of the impact of endometriosis symptoms on health-related quality of life and work productivity. *Fertil Steril* 2011;**96**:107–112.

Franke LC, Ament AJ, van de Laar MA, Boonen A, Severens JL. Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009;**27**:S118–S123.

Gao X, Outley J, Botteman M, Spalding J, Simon JA, Pashos CL. Economic burden of endometriosis. *Fertil Steril* 2006a;**86**:1561–1572.

Gao X, Yeh YC, Outley J, Simon J, Botteman M, Spalding J. Health-related quality of life burden of women with endometriosis: a literature review. *Curr Med Res Opin* 2006b;**22**:1787–1797.

Greiner W, Claes C, Busschbach JJ, von der Schulenburg JM. Validating the EQ-5D with time trade off for the German population. *Eur J Health Econ* 2005;**6**:124–130.

Gruppo italiano per lo studio dell'endometriosi. Prevalence and anatomical distribution of endometriosis in women with selected gynaecological conditions: results from a multicentric Italian study. *Hum Reprod* 1994;**9**:1158–1162.

Gylfason JT, Kristjansson KA, Sverrisdottir G, Jonsdottir K, Rafnsson V, Geirsson RT. Pelvic endometriosis diagnosed in an entire nation over 20 years. *Am J Epidemiol* 2010;**172**:237–243.

Houston DE, Noller KL, Melton LJ III, Selwyn BJ, Hardy RJ. Incidence of pelvic endometriosis in Rochester, Minnesota, 1970–1979. *Am J Epidemiol* 1987;**125**:959–969.

Hummelshoj L, Prentice A, Groothuis P. Update on endometriosis. *Womens Health* 2006;**2**:53–56.

Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;**10**:407–415.

Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005;**20**:2698–2704.

Kind P, Hardman G, Macran S. UK population norms for EQ-5D. In Centre for Health Economics. York: University of York, 1999.

Kjerulff KH, Erickson BA, Langenberg PW. Chronic gynecological conditions reported by US women: findings from the National Health Interview Survey, 1984 to 1992. *Am J Public Health* 1996;**86**:195–199.

Koster I, von Ferber L, Ihle P, Schubert I, Hauner H. The cost burden of diabetes mellitus: the evidence from Germany—the CoDiM study. *Diabetologia* 2006;**49**:1498–1504.

Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ* 2006;**15**:1121–1132.

Leardini G, Salaffi F, Montanelli R, Gerzeli S, Canesi B. A multicenter cost-of-illness study on rheumatoid arthritis in Italy. *Clin Exp Rheumatol* 2002;**20**:505–515.

Luo N, Johnson JA, Shaw JW, Feeny D, Coons SJ. Self-reported health status of the general adult U.S. population as assessed by the EQ-5D and health utilities index. *Med Care* 2005;**43**:1078–1086.

Mackin RS, Delucchi KL, Bennett RW, Arean PA. The effect of cognitive impairment on mental healthcare costs for individuals with severe psychiatric illness. *Am J Geriatr Psychiatry* 2011;**19**:176–184.

Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, D'Hooghe T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. *Fertil Steril* 2009;**92**:68–74.

Nnoaham KE, Hummelshoj L, Webster P, D'Hooghe T, de Cicco NF, de Cicco NC, Jenkinson C, Kennedy SH, Zondervan KT. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril* 2011;**96**:366–373.

Organisation for Economic Co-operation and Development. Purchasing power parities—comparative price levels. Organisation for Economic Co-operation and Development, Paris, 2009.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; **4**:353–365.

Shaw JW, Johnson JA, Chen S, Levin JR, Coons SJ. Racial/ethnic differences in preferences for the EQ-5D health states: results from the U.S. valuation study. *J Clin Epidemiol* 2007;**60**:479–490.

Simoens S, Hummelshoj L, D'Hooghe T. Endometriosis: cost estimates and methodological perspective. *Hum Reprod Update* 2007;**13**: 395–404.

Simoens S, Hummelshoj L, Dunselman G, Brandes I, Dirksen C, EndoCost Consortium. Endometriosis cost assessment (the EndoCost study): a cost-of-illness study protocol. *Gynecol Obstet Invest* 2011;**71**: 170–176.

Treloar SA, O'Connor DT, O'Connor VM, Martin NG. Genetic influences on endometriosis in an Australian twin sample. *Fertil Steril* 1999;**71**: 701–710.

Vessey MP, Villard-Mackintosh L, Painter R. Epidemiology of endometriosis in women attending family planning clinics. *Br Med J* 1993; **306**:182–184.

Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;**14**:1523–1532.

Wheeler JM. Epidemiology of endometriosis-associated infertility. *J Reprod Med* 1989;**34**:41–46.

World Bank. (2010) Population projection tables by country and group. Washington DC: World Bank (http://go.worldbank.org/KZHE1CQFA0).

Ying AK, Lairson DR, Giardino AP, Bondy ML, Zaheer I, Haymond MW, Heptulla RA. Predictors of direct costs of diabetes care in pediatric patients with type 1 diabetes. *Pediatr Diabetes* 2011;**12**(Pt 1):177–182.

Yu AP, Cabanilla LA, Wu EQ, Mulani PM, Chao J. The costs of Crohn's disease in the United States and other Western countries: a systematic review. *Curr Med Res Opin* 2008;**24**:319–328.